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Early View

Research letter

Steroid use in elderly critically ill COVID-19 patients

Christian Jung, Bernhard Wernly, Jesper Fjølner, Raphael Romano Bruno, David Dudzinski, Antonio Artigas, Bernardo Bollen Pinto, Joerg C. Schefold, Georg Wolff, Malte Kelm, Michael Beil, Sviri Sigal, Peter Vernon van Heerden, Wojciech Szczeklik, Miroslaw Czuczwar, Muhammed Elhadi, Michael Joannidis, Sandra Oeyen, Tilemachos Zafeiridis, Brian Marsh, Finn H. Andersen, Rui Moreno, Maurizio Cecconi, Susannah Leaver, Ariane Boumendil, Dylan W. De Lange, Bertrand Guidet, Hans Flaatten, COVIP study group (see appendix 1, covip@med.uni-duesseldorf.de)

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Steroid use in elderly critically ill COVID-19 patients

Christian Jung (1) Christian.jung@med.uni-duesseldorf.de ,

Bernhard Wernly (2) b.wernly@salk.at ,

Jesper Fjølner (3) jespfjoe@rm.dk ,

Raphael Romano Bruno (1) Raphael.Bruno@med.uni-duesseldorf.de ,

David Dudzinski (4) ddudzinski@mgh.harvard.edu

Antonio Artigas (5) AArtigas@tauli.cat ,

Bernardo Bollen Pinto (6) Bernardo.BollenPinto@hcuge.ch ,

Joerg C. Schefold (7) joerg.schefold@insel.ch ,

Georg Wolff (1) Georg.wolff@med.uni-duesseldorf.de ,

Malte Kelm (1) malte.kelm@med.uni-duesseldorf.de ,

Michael Beil (8) beil@doctors.org.uk ,

Sviri Sigal (8) Sigals1@hadassah.org.il ,

Peter Vernon van Heerden (9) vernon@hadassah.org.il ,

Wojciech Szczeklik (10) wojciech.szczeklik@uj.edu.pl ,

Miroslaw Czuczwar (11) czuczwarm@gmail.com ,

Muhammed Elhadi (12) muhammed.elhadi.uot@gmail.com ,

Michael Joannidis (13) michael.joannidis@tirol-kliniken.at ,

Sandra Oeyen (14) sandra.oeyen@ugent.be ,

Tilemachos Zafeiridis (15) tilemachos@hotmail.com ,

Brian Marsh (16) bmarsh@mater.ie ,

Finn H. Andersen (17) Finn.H.Andersen@helse-mr.no ,

Rui Moreno (18) r.moreno@mail.telepac.pt ,

Maurizio Cecconi (19) maurizio.cecconi@hunimed.eu ,

Susannah Leaver (20) susannahleaver@nhs.net ,

Ariane Boumendil (21) ariane.boumendil@gmail.com ,

Dylan W. De Lange (22) D.W.deLange-3@umcutrecht.nl ,

Bertrand Guidet (21) bertrand.guidet@aphp.fr ,

Hans Flaatten (23) Hans.Flaatten@uib.no ,

COVIP study group (see appendix 1, covip@med.uni-duesseldorf.de)

Affiliations

1. Heinrich-Heine-University Duesseldorf, Medical Faculty, Department of Cardiology, Pulmonology and Vascular Medicine, Duesseldorf, Germany
2. Department of Anaesthesiology, Perioperative Medicine and Intensive Care Medicine, Paracelsus Medical University, Salzburg, Austria
3. Department of Intensive Care, Aarhus University Hospital, Aarhus, Denmark
4. Cardiac Intensive Care Unit, Massachusetts General Hospital, Boston, USA
5. Department of Intensive Care Medicine, CIBER Enfermedades Respiratorias, Corporacion Sanitaria Universitaria Parc Tauli, Autonomous University of Barcelona, Sabadell, Spain
6. Department of Acute Medicine, Geneva University Hospitals, Geneva, Switzerland
7. Department of Intensive Care Medicine, Inselspital, Universitätsspital, University of Bern, Bern, Switzerland
8. Department of Medical Intensive Care, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Israel
9. Department of Anesthesia, Intensive Care and Pain Medicine, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Israel
10. Center for Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Poland
11. 2nd Department of Anesthesiology and Intensive Care, Medical University of Lublin, Staszica 16, 20-081, Lublin, Poland
12. Faculty of Medicine, University of Tripoli, Tripoli, Libya
13. Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria

14. Department of Intensive Care 1K12IC Ghent University Hospital, Ghent, Belgium
15. Intensive Care Unit General Hospital of Larissa, Larissa, Greece
16. Mater Misericordiae University Hospital, Dublin, Ireland
17. Dep. Of Anaesthesia and Intensive Care, Ålesund Hospital, Ålesund, Norway. Dep. of Circulation and medical imaging, Norwegian university of Science and Technology, Trondheim, Norway
18. Unidade de Cuidados Intensivos Neurocríticos e Trauma. Hospital de São José, Centro Hospitalar Universitário de Lisboa Central, Faculdade de Ciências Médicas de Lisboa, Nova Médical School, Lisbon, Portugal
19. Department of Anaesthesia IRCCS Instituto Clínico Humanitas, Humanitas University, Milan, Italy
20. General Intensive care, St George´s University Hospitals NHS Foundation trust, London, United Kingdom
21. Sorbonne Universités, UPMC Univ Paris 06, INSERM, UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe: épidémiologie hospitalière qualité et organisation des soins, F-75012, Paris, France. Assistance Publique - Hôpitaux de Paris, Hôpital Saint-Antoine, service de réanimation médicale, Paris, F-75012, France
22. Department of Intensive Care Medicine, University Medical Center, University Utrecht, the Netherlands
23. Department of Clinical Medicine,University of Bergen, Department of Anaestesia and Intensive Care, Haukeland University Hospital , Bergen, Norway

Corresponding author:

Christian Jung, M.D. PhD

Division of Cardiology, Pulmonology, and Vascular Medicine

Medical Faculty, University Duesseldorf

Moorenstraße 5, 40225 Duesseldorf, Germany

Email: christian.jung@med.uni-duesseldorf.de

Twitter: cjungMD

Tweet:

This secondary analysis of the COVIP study shows a higher 30-day-mortality in critically ill elderly COVID-19 patients who received steroids as part of their treatment.

Background

More than a year after the onset of the SARS-Cov-2 pandemic, treating patients with COVID-19 remains a challenge. By contrast to the rapid development of effective vaccines against SARS-Cov-2, the development of specific and effective therapeutics against COVID-19 remains largely unresolved.

In addition to standard intensive care, including oxygen therapy and organ support when required, the use of systemic corticosteroids was found to have a positive effect in randomised trials. However, data from treating elderly COVID-19 patients are scarce.

Importantly, treatment with corticosteroids has well documented deleterious effects [1]: While the immunosuppressive effect in patients with COVID-19 is presumably responsible for the desired therapeutic effect, it may also render the patients more prone to secondary bacterial infections and potentially decrease viral clearance [2]. Corticosteroid therapy is also associated with hyperglycemia, has catabolic effects and is associated with neuropathy. This could potentially affect the risk-benefit balance, especially in vulnerable patient groups such as elderly, frail patients.

Objective

The aim of this secondary analysis was to investigate the effects of corticosteroid therapy in an international observational prospective study of critically ill elderly patients with COVID-19.

Methods

The COVIP study ("Corona Virus disease (COVID19) in Very Elderly Intensive care Patients (VIPs)" - COVIP study (NCT04321265)) included patients aged 70 years or older with proven COVID-19 and admitted to an intensive care unit (ICU) [3]. 30-day-mortality was defined as the primary endpoint. The study was conducted by the Very old Intensive care Patient (VIP) network [4] across 207 ICUs in 35 countries. Data were collected through an electronic case report form. A prospective study design was chosen to achieve high-quality data. Informed consent was taken if not waived by the local ethical committee.

Two multi-level logistic regression models were utilised: The first model used the hospital unit as random effect and the steroid use as fixed effect. The second model was a multi-variable model adjusting for "The Sequential Organ Failure Assessment" (SOFA) score and frailty as assessed by the Clinical Frailty Scale (CFS). Sensitivity analyses complemented the analysis.

Results

In total, 3082 patients were included in the COVIP study, 2115 patients received corticosteroids, and 967 patients received none. Median age was 75 (IQR 72-79] years in both groups. With a median SOFA score of 5 (IQR 3-8), there was no difference between the two groups.

30-day mortality was 53% in the group treated with corticosteroids and 42% in the no-corticosteroid group (p<0.001).

The univariate 30-day-mortality rates were higher in patients receiving corticosteroids (53 vs. 42%; aOR 1.16; 95%CI 1.28-2.02; p<0.001). This association of corticosteroid use was even more pronounced after 3 months (69% vs 49%; p<0.001; Figure 1A). In addition, we found that corticosteroids remained associated with increased odds of 30-day-mortality after multivariable adjustment (aOR 1.60 95%CI 1.26-2.04; <0.001). Further sensitivity analyses consistently confirmed the finding in subgroups stratifying for age (Figure 1B. <80/≥80 years), frailty (fit/vulnerable/frail), mechanical ventilation (yes/no), non-invasive ventilation (yes/no), sex (female/male), symptom onset (≤7days/>7days), and vasopressor therapy (yes/no)- Furthermore, in sensitivity analyses evaluating patients in the first surge (March-May, aOR 1.38 95%CI 1.05-1.82; p=0.02; n=1448) and the second surge (September-December, aOR 2.09 95%CI 1.04-4.21; p=0.04; n=1414) the finding was sustained.

Discussion

In this prospective study of more than 3000 critically ill COVID-19 patients age 70 years and older, we have found an independent association of steroid use with increased mortality.

These results question the routine use of corticosteroid treatment in elderly COVID-19 patients. While the immunosuppressive effect of steroids is undisputed and desirable in the context of severe COVID-19 treatment, the adverse effects of steroid treatment in elderly patients may outweigh the potential benefits.

This is the largest prospective analysis of critically ill elderly patients in relation to corticosteroid use to treat severe COVID-19 disease. Corticosteroid therapy has been established as standard of care in all ICU patients. However, even landmark randomised controlled trials do not support this with evidence in elderly patients. The RECOVERY study [5] showed no effect of corticosteroids in their subgroup of patients >70 years. Of note, only 169 patients in this group were on mechanical ventilation. The CoDEX study found no effect

on mortality after 28 days, but no data was supplied specifically looking at patients above 70 years old.[6] Thus, both studies included far fewer patients than our current analysis. It is important to note that our data does not question the corticosteroid strategy in younger COVID-19 patients. It just emphasises that the decision to use corticosteroids needs to be individually tailored, first and foremost according to age, but also with regards to comorbidities and other factors.[7]

Our analysis has limitations: First, this is a secondary analysis of a prospective study. Second, our study is not randomised and despite multivariable adjustment, it is likely that unknown confounding factors may have contributed to our findings. Third, we have no detailed information about dosage and duration of corticosteroid treatment.

In conclusion, in this prospective observational study we found a higher 30-day-mortality in critically ill elderly COVID-19 patients who received steroids as part of their treatment.

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Figure legend:

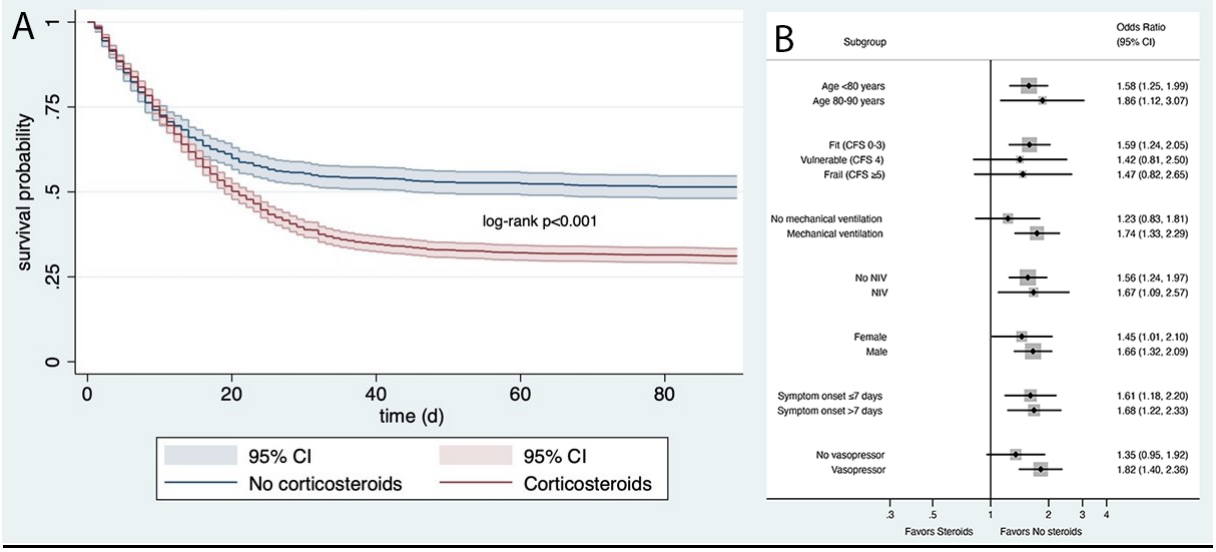

Figure 1:

A: Plot of the Kaplan–Meier estimator illustrating survival probability up to 90 days after admission to the intensive care unit for patients with and without corticosteroid treatment. Log-rank-test: p<0.001. Abbreviations: CI: Confidence interval. d: days

B: Sensitivity analyses stratifying 30-day-mortality in subgroups for patient-specific characteristics and management strategies using multi-level logistic regression models. We depicted aORs from the model with the hospital unit as random effect and the steroid use as fixed effect. CFS: Clinical frailty scale; NIV: non-invasive ventilation; CI: Confidence interval.